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(71) Applicant (for all designated States except US): DARWIN DISCOVERY LIMITED [GB/GB]; Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB).			
(72) Inventors; and (75) Inventors/Applicants (for US only): GILBERT, Julian, Clive [GB/GB]; Darwin Discovery Limited, Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB). RICHARDS, Andrew, John, McGlashan [GB/GB]; Darwin Discovery Limited, Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB). BARDSELEY, Hazel, Judith [GB/GB]; Darwin Discovery Limited, Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB).			
(74) Agent: GILL JENNINGS & EVERY; Broadgate House, 7 Eldon Street, London EC2M 7LH (GB).			

(54) Title: DOSAGE FORMS COMPRISING SEPARATE PORTIONS OF R- AND S-ENANTIOMERS

## (57) Abstract

A pharmaceutical dosage form comprises, in one portion thereof, a substantially single (+)-enantiomer of a chiral drug other than verapamil and, in another separate portion thereof, a substantially single (-)-enantiomer of the drug, wherein, in use, the different enantiomers are released at different rates from the dosage form. The dosage form is useful for administration of chiral drugs where both enantiomers have a valid pharmacological input, and where a clinical benefit may be realised by controlling the release rates of those enantiomers. Examples of such drugs include, in particular, tramadol and warfarin.

## Published

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## DOSAGE FORMS COMPRISING SEPARATE PORTIONS OF R- AND S-ENANTIOMERS

Field of the Invention

5 This invention relates to the discovery of novel pharmaceutical dosage forms of chiral drugs.

Background to the Invention

10 The separate enantiomers of some chiral drugs have different therapeutic properties, and/or mechanisms of action and yet in some cases it may still be desirable to dose both enantiomers together. However, where the pharmacokinetic properties of the separate enantiomers are different, for instance due to differences in the rates at which they are metabolised, the ratio of the different enantiomers changes with time after initial dosing, which 15 can lead to reduced efficacy of the drug. The actual enantiomeric ratio at any one time may be dependent upon a number of factors, and may be further complicated if different dosage forms provide different enantiomeric ratios. Effects such as these have been observed with the 20 different enantiomers of verapamil, for instance see Longstreth, J.A. Clin. Pharmacol. (1993) 18 (2nd Edition): 315-336 and Gupta et al., Eur. J. Pharm. Biopharm. (1996) 42(1): 74-81.

Summary of the Invention

25 According to the present invention, a pharmaceutical dosage form comprises, in one portion thereof, a substantially single (+)-enantiomer of a chiral drug other than verapamil and, in another, separate, portion thereof, a substantially single (-)-enantiomer of the drug, wherein, 30 in use, the different enantiomers are released at different rates from the dosage form.

Where the different enantiomers of the chiral drug are absorbed, metabolised, distributed or secreted by the body at different rates, their rates of release from the dosage 35 form may be arranged such that their initial ratio, whether this is 50:50 or a non-racemic ratio, is maintained, ideally throughout the dosing period. By manipulating the

administration of the different enantiomers in this way, presentation of the desired enantiomer to the target organ is optimised, thereby increasing the clinical efficacy of the drug throughout the dosing period.

5 The present invention may also be beneficial in administering chiral drugs whose individual enantiomers have different efficacies, different modes of action, different selectivities, e.g. to receptors or enzymes, or different toxicities.

10 The present invention may also be beneficial in administering chiral drugs which have a side effect associated therewith, but where the side effect resides in only one of the drug's two individual enantiomers. In this case, it may be desirable to have a different release rate 15 for the enantiomer causing the side effect, although this will depend upon the nature of the side effect.

20 Examples of chiral drugs where both enantiomers have a valid pharmacological input, and where a clinical benefit may be realised by controlling the release rates of those enantiomers, include warfarin, tramadol, mianserin, carvedilol, citalopram, dobutamine, aminoglutethimide, alfuzosin, celiprolol, cisapride, disopyramide, fenoldopam, flecainide, hydroxychloroquine, ifosfamide, labetolol, mexiletine, propafenone, tegafur, terazosin, thioctic acid, 25 thiopental and zacopride, and in particular warfarin and tramadol, and most particularly tramadol.

Description of the Invention

30 The present invention covers any dosage form in which the two enantiomers of a chiral drug are physically separated, or compartmentalised, so as to achieve different release rates of the different enantiomers. Such separation, or compartmentalisation, may be on a macro-scale, for instance with the different enantiomers being incorporated into separate dosage forms for simultaneous or 35 sequential administration, i.e. as a kit, or separation of the different enantiomers may be on a micro-scale, for instance with the different enantiomers being present

within the same dosage form and despite their physical separation being intimately mixed, or somewhere intermediate the two.

In the context of this Application, by substantially single enantiomer typically we mean that one enantiomer is in an excess of at least 70% by weight with respect to the other enantiomer, and is preferably in an excess of at least 80%, and more preferably 90%, or higher. Furthermore, by a non-racemic ratio of enantiomers typically we mean that both enantiomers are present, with either the (-)-enantiomer being present in an amount in excess of that of the (+)-enantiomer, or vice versa.

A number of release profiles for the different enantiomers of a chiral drug may be realised by way of the dosage forms of the present invention. For instance, a dosage form may be designed to allow immediate release of one enantiomer and sustained, or controlled, release of the other enantiomer. In this case, by immediate release typically we mean that release of the respective enantiomer occurs substantially immediately or after only a short delay, usually no more than five to ten minutes, after administration of the dosage form, and continues usually over a period of up to one to two hours. By sustained, or controlled, release typically we mean that release of the respective enantiomer is delayed usually for at least one hour and frequently longer, for instance for two or more hours, after administration of the dosage form. The sustained, or controlled, release may be constant or variable throughout the treatment period.

The dosage forms of the present invention may be designed to release either of the enantiomers faster than the other, or before the other, depending upon the condition to be treated, or the patient type. It may be desirable to maintain a constant ratio of the separate enantiomers at the target tissue over a specified period of time, for instance at least 8 hours a day, preferably at least 12 hours a day, most preferably 24 hours a day. The

ratio maintained may be 50:50, or a non-racemic ratio in which either the amount of the (+)-enantiomer is greater than the (-)-enantiomer, or vice versa.

Another option would be to vary the ratio of the two enantiomers throughout the treatment period, or at least for a portion of that period. For instance, the release rate of either or both enantiomers can be arranged to vary, so that either the relative proportion of the (+)-enantiomer or of the (-)-enantiomer increases, or decreases, with time. The latter may be achieved, for instance, by using a number of different release coatings for the respective enantiomer.

As mentioned above, the present invention may have particular application in the administration of tramadol and warfarin. Tramadol is formulated as the racemate for use as a high-potency analgesic with opioid-like properties. The analgesic efficacy and safety of the racemate and the individual enantiomers have been investigated in a randomised, double-blind study with gynaecological patients using intravenous patient-controlled analgesia (see Grond, S, et al. Pain (1995) 62(3):313-320). Although (+)-tramadol appeared to be more potent in producing analgesia, it also produced more nausea and vomiting. Since the racemate has more efficacy than (-)-tramadol and no more side effects than (+)-tramadol, the authors concluded that the racemate had more clinical utility. In another study it was shown that there is complementary and synergistic antinociceptive interaction between the individual enantiomers of tramadol (see Raffa, R.B. et al. J Pharmacol. Exp. Ther. (1993) 267(1): 331-340). The enantiomers have different potencies at opioid receptors, and in inhibiting serotonin re-uptake and noradrenaline re-uptake. It therefore appears that both enantiomers of tramadol contribute to the analgesic effect. Thus, it is possible that controlled administration of the individual enantiomers at different rates, facilitated by the dosage form embodied by the present invention, could

result in even more useful analgesia without additional side effects.

5 A preferred dosage form for administration of tramadol is one in which (-)-tramadol is in immediate-release form and (+)-tramadol is in a sustained-, or controlled-, release form. In this case, the release rate of the (+)-enantiomer could be controlled in such a way to reduce the adverse side effects of nausea and/or dizziness believed to be associated with that enantiomer.

10 In the case of the anticoagulant drug warfarin, which is currently formulated as the racemate for clinical use, both the (*S*)--(--) and (*R*)--(+) enantiomers exhibit the desired hypoprothrombinemic activity, with (*S*)-warfarin being the more potent (see Hyneck, M. et al, Chirality in Drug Design and Synthesis (1990), p. 17-18, ed. C. Brown, Academic Press, London). However, use of warfarin in this form, i.e. as the racemate, is complicated by a delay of a few days before the onset of the desired anticoagulant effect. Thus, once therapy has commenced, careful 15 monitoring is necessary to strike a balance between underdosing and overdosing; overdosing may lead to haemorrhage and may sometimes be fatal. This effect may be attributable to the individual enantiomers of warfarin having different affinities for albumin binding, and their 20 being metabolised by different pathways which in turn will influence relative clearance rates. Thus, administration of separate formulations of the individual enantiomers, or a simple formulation in which the individual enantiomers are separated, may achieve a more controllable treatment 25 regime.

30 A number of different types of dosage form can be envisaged, for administration by a variety of routes, e.g. oral, rectal, transdermal, nasal, ophthalmic, pulmonary and injectable (subcutaneous or intravenous).

35 The Applicant's co-pending Application WO 97/33570, describes dosage forms from which the individual enantiomers of verapamil are released at different rates,

and any of these may be employed with any of the above drugs.

For instance, one type of dosage form comprises a capsule containing two sets of multiparticulates having different release rates, one set containing the (+)-enantiomer and the other set containing the (-)-enantiomer. The multiparticulates themselves can be made by any of the conventional methods, including extrusion spheronisation, high shear granulation, non-pareil seeds, etc. The rates at which the different enantiomers are released from the multiparticulates can be achieved using any conventional controlled-release mechanism, for instance, matrix (ie. erosion diffusion), coating, or osmotic. Dosage forms of this type are suitable for oral and rectal use.

Another type of dosage form comprises two tablets, i.e. as a combined product (kit), one tablet containing the (+)-enantiomer and the other tablet containing the (-)-enantiomer, the two tablets having different release rates. Again, conventional control-release technology can be used to achieve the desired effect. For example, two tablets having different release coatings or matrices may be used, or two osmotic pump tablets having different pumping rates. The tablets can then be administered in sequence, or they can be filled into a capsule for dosing simultaneously.

Another type of dosage form comprises an osmotic pump tablet comprising two distinct portions, typically two layers, one portion containing and pumping the (+)-enantiomer at one rate, and the other portion containing and pumping the (-)-enantiomer at another rate.

Another type of dosage form comprises a bi-layered tablet, one layer containing the (+)-enantiomer and the other layer containing the (-)-enantiomer, the two layers having different release rates for their respective enantiomers. Again, conventional control-release technology can be used to achieve the desired effect.

One example of a bi-layered tablet may have (-)-tramadol in an outer layer as a starter treatment, leading

on to release of (+)-tramadol from the core which would provide maintenance therapy. Another example of a bilayered tablet may have (S)-warfarin in an outer layer as a starter treatment, and (R)-tramadol in a core for maintenance therapy. Different percentages of the individual enantiomers could be used in different tablet preparations so that doses could be titrated for individuals.

Another type of dosage form comprises a compressed coat tablet having a core containing one of the (+)- and (-)-enantiomers and, surrounding the core, a shell containing the other of the (+)- and (-)-enantiomers, the core and shell having different release rates for their respective enantiomers.

Another type of dosage form comprises a patch for placing adjacent a patient's skin, the patch comprising two distinct portions, one portion containing the (+)-enantiomer and the other portion containing the (-)-enantiomer, the two portions having different release rates for their respective enantiomers. Alternatively, two separate patches may be used, i.e. as a combined product (kit), one patch containing the (+)-enantiomer and the other patch containing the (-)-enantiomer, the two patches having different release rates.

Another type of dosage form comprises a polymer implant comprising two distinct portions, one portion containing the (+)-enantiomer and the other portion containing the (-)-enantiomer, the two portions having different release rates for their respective enantiomers. Alternatively, two separate polymer implants may be used, i.e. as a combined product (kit), one implant containing the (+)-enantiomer and the other implant containing the (-)-enantiomer, the two implants having different release rates.

Another type of dosage form comprises an aerosol containing two sets of microparticles having different release rates, one set containing the (+)-enantiomer and

the other set containing the (-)-enantiomer. Alternatively, two separate aerosols may be used, one for each enantiomer, i.e. as a combined product (kit), the microparticles of each aerosol having different release rates.

5 Other types of dosage form may be for administration by injection. With dosage forms of this type, different release rates of the different enantiomers may be achieved by means of, for example, liposomes or microparticulates.

10 As, in the present invention, the two enantiomers are effectively dosed separately, it is essential that they are provided in a form that is not harmful to the prospective patient. If they are provided in salt form, both salts should preferably be stable and non-hygroscopic.

15 The dosage forms of the present invention can be used in the treatment of conditions for which the chiral drug is usually administered, particularly in patients disposed to, or who may be put at risk by exposure to, an adverse side effect.

20 The present invention is now illustrated by way of the following Examples.

Examples

25 In the following, tablets were prepared using a Universal Testing Instrument (Instron floor model, Instron Limited, High Wycombe, United Kingdom) at a compression rate of 1 mm/min, using a tabletting pressure of 200 MPa, and an 8 mm flat-faced punch.

30 The disintegration properties of the tablets were assessed in a disintegration tester (Erweka GmbH, Heusenstamm Germany) according to BP using water at  $37^{\circ}\text{C} \pm 0.2$  K. The dissolution profiles of the tablets were evaluated employing the USP XXIII paddle method (Pharmatest, Hamburg, Germany) using 1000 ml distilled water at  $37^{\circ}\text{C} \pm 0.5$  K and a paddle speed of 100 rpm. The dissolved amount of drug, whether (+)- or (-)-tramadol hydrochloride, was measured with on-line UV (Phillips PU 8620, Hamburg, Germany) at a wavelength of 220 nm.

In the accompanying Figures, Figures ■ represents (+)-tramadol hydrochloride and □ represents (-)-tramadol hydrochloride.

Example 1

5 Immediate-release tablets were prepared from a powder mixture of 50.0 mg (+)- or (-)-tramadol hydrochloride, 46.5 mg microcrystalline cellulose, 3.0 mg croscarmellose sodium and 0.5 mg magnesium stearate, using a tabletting pressure of 200 MPa. Disintegration was monitored over 30 minutes.

10 The drug release from the immediate-release tablets is depicted in Figure 1, with the y-axis showing the concentrations of the individual enantiomers in the dissolution medium. The dissolution pattern observed guarantees a rapid pharmaceutical availability of the drug.

Example 2

15 Controlled-release tablets were prepared from a powder mixture of 50.00 mg (+)- or (-)-tramadol hydrochloride, 119.15 mg hydroxypropyl methyl cellulose (HPMC) and 0.85 mg magnesium stearate, using a tabletting pressure of 200 MPa. Disintegration was monitored over a period of 7 hours.

20 The drug release of the controlled-release tablets is depicted in Figure 2, as a dissolution profile, with the y-axis showing the concentrations of the individual enantiomers in the dissolution medium, and in Figure 3 as a percentage of drug release. A twelve hour controlled-release was achieved with the present formulation. After 25 6 hours, the (-)-enantiomer is released slightly faster than the (+)-enantiomer, achieving nearly 100% drug release at 12 hours, whereas only 86% of the (+)-enantiomer was released after 12 hours. Below 6 hours, the drug release profiles of the two enantiomers were very similar.

Example 3

25 Bi-layered tablets were prepared by pre-compressing the powder mixture of Example 2 at a tabletting pressure of 20 MPa to form a controlled-release layer. The powder mixture of Example 1, containing the opposite enantiomer of tramadol hydrochloride to that used in the controlled-

release layer, was then filled on top of the controlled-release layer, and the whole tablet compressed using a tabletting pressure of 200 MPa.

The dissolution profiles of the individual layers of the bi-layered tablets were obtained by chiral HPLC analysis of tramadol free base using a Chiralpak AD Column (eluent 90% heptane, 9.99% isopropanol, 0.01% diethylamine), on which (+)-tramadol had a retention time of 4.5 minutes and (-)-tramadol a retention time of 5.6 minutes, and are depicted in Figure 4, in which the y-axis shows the concentration of the individual enantiomers in the dissolution medium.

Shorter release profiles from a controlled-release layer may be achieved simply by altering the amount of the excipients used, and in the present case by lowering the amount of HPMC. Furthermore, if increased dosage is required, the tablet diameter may be increased.

CLAIMS

1. Pharmaceutical dosage form comprising, in one portion thereof, a substantially single (+)-enantiomer of a chiral drug other than verapamil and, in another, separate, portion thereof, a substantially single (-)-enantiomer of the drug, wherein, in use, the different enantiomers are released at different rates from the dosage form.  
5
2. Dosage form according to claim 1, wherein the chiral drug is any drug whose different enantiomers are absorbed, metabolised, distributed or secreted by the body at different rates.  
10
3. Dosage form according to claim 1 or claim 2, wherein the chiral drug is any drug whose different enantiomers have different efficacies or different modes of action.  
15
4. Dosage form according to claim 1 or claim 2, wherein the chiral drug is any drug having an adverse side effect residing in one of its two enantiomers.
5. Dosage form according to any preceding claim, wherein the release rates of the different enantiomers are selected to give a substantially constant ratio of those enantiomers at a target tissue for at least 8 hours in a day.  
20
6. Dosage form according to claim 5, wherein the ratio of the enantiomers at the target tissue is about 50:50.
7. Dosage form according to claim 5, wherein the ratio of the enantiomers at the target tissue is a non-racemic ratio, with the (+)-enantiomer in excess compared with the (-)-enantiomer.  
25
8. Dosage form according to claim 5, wherein the ratio of the enantiomers at the target tissue is a non-racemic ratio, with the (-)-enantiomer being in excess compared with the (+)-enantiomer.  
30
9. Dosage form according to claim 1, wherein at least the release rate of one of the enantiomers varies with time.
- 35 10. Dosage form according to claim 9, wherein the rate of release of the (+)-enantiomer increases or decreases with time.

11. Dosage form according to claim 12, wherein the rate of release of the (-)-enantiomer increases or decreases with time.
- 5 12. Dosage form according to claim 1, from which the (+)-enantiomer is released faster than the (-)-enantiomer.
13. Dosage form according to claim 1, from which the (-)-enantiomer is released faster than the (+)-enantiomer.
- 10 14. Dosage form according to any preceding claim, which comprises a capsule containing a plurality of first particles containing the (+)-enantiomer and a plurality of second particles containing the (-)-enantiomer, the first and second particles having different release rates for their respective enantiomers.
- 15 16. Dosage form according to any of claims 1 to 13, which comprises a first tablet containing the (+)-enantiomer and a second tablet containing the (-)-enantiomer, the first and second tablets having different release rates for their respective enantiomers.
- 20 17. Dosage form according to any of claims 1 to 13, which comprises an osmotic pump tablet having a first portion containing the (+)-enantiomer and a second portion containing the (-)-enantiomer, wherein the first and second portions have different pumping rates for their respective enantiomers.
- 25 18. Dosage form according to any of claims 1 to 13, which comprises a bi-layered tablet, one layer containing the (+)-enantiomer and the other layer containing the (-)-enantiomer, the two layers having different release rates for their respective enantiomers.
- 30 19. Dosage form according to any of claims 1 to 13, which comprises a compressed coat tablet having a core containing one of the (+)- and (-)-enantiomers and, surrounding the core, a shell containing the other of the (+)- and (-)-enantiomers.
- 35

20. Dosage form according to any of claims 1 to 13, which comprises a patch for placing adjacent a patient's skin, the patch comprising a first portion containing the (+)-enantiomer and a second portion containing the (-)-enantiomer, the first and second portions having different release rates for their respective enantiomers.
- 5
21. Dosage form according to any of claims 1 to 13, which comprises two patches, each for placing adjacent a patient's skin, one patch containing the (+)-enantiomer and the other patch containing the (-)-enantiomer, the two patches having different release rates.
- 10
22. Dosage form according to any of claims 1 to 13, which comprises a polymer implant having a first portion containing the (+)-enantiomer and a second portion containing the (-)-enantiomer, wherein the first and second portions have different release rates for their respective enantiomers.
- 15
23. Dosage form according to any of claims 1 to 13, which comprises two polymer implants, one implant containing the (+)-enantiomer and the other implant containing the (-)-enantiomer, the two implants having different release rates.
- 20
24. Dosage form according to any of claims 1 to 13, which comprises an aerosol containing two sets of microparticles having different release rates, one set containing the (+)-enantiomer and the other set containing the (-)-enantiomer.
- 25
25. Dosage form according to any of claims 1 to 13, which comprises two aerosols, one containing microparticles containing the (+)-enantiomer and the other containing microparticles containing the (-)-enantiomer, the microparticles in the two aerosols having different release rates for their respective enantiomers.
- 30
26. Dosage form according to any preceding claim, wherein the chiral drug is selected from warfarin, tramadol, mianserin, carvedilol, citalopram, dobutamine and aminoglutethimide.
- 35

27. Dosage form according to claim 26, wherein the chiral drug is warfarin.
28. Dosage form according to claim 26, wherein the chiral drug is tramadol.
- 5 29. Dosage form according to claim 28, wherein (-)-tramadol is in immediate release form and (+)-tramadol is in sustained release form.
- 10 30. Dosage form according to claim 28 or 29, which is a bi-layered tablet having an outer layer comprising (-)-tramadol and a core comprising (+)-tramadol.
- 15 31. Dosage form according to any of claims 1 to 25, wherein the chiral drug is selected from alfuzosin, celiprolol, cisapride, disopyramide, fenodopam, flecainide, hydroxychloroquine, ifosfamide, labetolol, mexiletine, propafenone, tegafur, terazosin, thioctic acid, thiopental and zacopride.
- 20 32. Dosage form according to any of claims 1 to 25, wherein the chiral drug is any drug whose different enantiomers have different selectivities.
- 25 33. Dosage form according to any of claims 1 to 25, wherein the chiral drug is any drug whose different enantiomers have different toxicities.
34. Dosage form according to any of claims 1 to 27, and 31 to 33, wherein one enantiomer is in immediate release form and the other enantiomer is in sustained release form.
35. Use of the substantially single enantiomers of a chiral drug in the manufacture of a dosage form as defined in any preceding claim, for the treatment of a condition for which that drug is usually administered in racemic form, in a patient who is either disposed to, or who would be put at risk by exposure to, an adverse side effect.

## INTERNATIONAL SEARCH REPORT

International Application No  
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A. CLASSIFICATION OF SUBJECT MATTER  
 IPC 6 A61K9/22 A61K9/50 A61K9/70

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
 IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 00075 A (CHIROSCIENCE LTD ;WAINER IRVING WILLIAM (CA); GRANVIL CAMILLE PIER) 4 January 1996  see page 4, line 3 - line 37 see page 4, line 30 - page 5, line 10 see page 11, line 3 - line 37 see claims 1,2 ---	1-4, 9-11, 14-16, 32,33,35
X	US 5 204 116 A (EDGREN DAVID E ET AL) 20 April 1993 see column 1, line 66 - column 2, line 36 see column 4, line 43 - line 61 ---	1,35
A	DE 43 19 438 C (GEISLINGER GERD DR DR ;BRUNE KAY PROF DR (DE)) 1 June 1994 see page 6, line 25 - line 67 ---	1 -/-

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European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Boulois, D

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I. International Application No  
PCT/GB 98/00726

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 818 541 A (SANDERSON JOHN E) 4 April 1989 see column 3 - column 4; examples 1,2 -----	1

3

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

**INTERNATIONAL SEARCH REPORT**

international application No.

PCT/GB 98/00726

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: 1 and 35 because they relate to subject matter not required to be searched by this Authority, namely:  
See FURTHER INFORMATION SHEET PCT/ISA/210
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking(Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**

International Application No. PCT/ GB 98/00726

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

In view of the large number of compounds which are theoretically defined by the expression "chiral drug" in claims 1 and 35, the search has been restricted for economic reasons. The search was limited to the general concepts of "chiral drug", "enantiomers", to the compounds cited in the examples and in the description (see page 2, lines 20-26) and claimed in Claims 26 and 31 (PCT Search Guidelines PCT/GL2, Chapter III, 2.1., 3.6. and 3.7.).

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No  
PCT/GB 98/00726

Patent document cited in search report	Publication date		Patent family member(s)		Publication date
WO 9600075 A	04-01-1996		AU 7789394 A CA 2170136 A		19-01-1996 04-01-1996
US 5204116 A	20-04-1993		US 5338550 A		16-08-1994
DE 4319438 C	01-06-1994		AU 6927294 A WO 9428890 A		03-01-1995 22-12-1994
US 4818541 A	04-04-1989		NONE		

Form PCT/ISA/210 (patent family annex) (July 1992)